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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,056	07/12/2001	Avi Ashkenazi	10466/81	2902

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,056	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44-47 and 49-51* is/are allowed.

6)☒ Claim(s) *39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 September 2004 has been entered in full.

Claims 1-38 and 48 are canceled. Claims 39-47 and 49-51 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. § 112, First Paragraph

Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% sequence identity to the polypeptide of SEQ ID NO: 292 or the mature form thereof or the extracellular domain thereof, which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells, does not reasonably provide enablement for other variants of SEQ ID NO: 292. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate

in scope with these claims. The basis for this rejection is of record and can be found, for example, at pp. 2-5 of the previous Office Action (mailed 30 March 2004).

Applicant's arguments (pp. 6-7 of preliminary amendment received 30 September 2004) have been fully considered but are not found to be persuasive for the following reasons. The Fong declaration under 37 CFR 1.132 filed 30 September 2004 is insufficient to overcome the rejection of claims 39-43 based upon 35 U.S.C. § 112, first paragraph (enablement) as set forth in the last Office action for the following reasons.

Applicant argues that the inflammation observed in Assay #64 (the skin vascular permeability assay) was not due to an irritant or allergic response because the PRO331 molecule was injected into a non-presensitized animal. This has been fully considered but is not found to be persuasive. If any type of irritant (including lye or acid) is injected under the skin of a non-presensitized animal, a positive result would be observed in Assay # 64. Thus, a positive result in the assay does not provide the skilled artisan with any information other than that the injected substance was an irritant.

Applicant refers to the declaration of Dr. Fong, submitted with the response under 37 CFR § 1.132. In the declaration, items 1-9, Dr. Fong states that Assay # 64 is known as the Miles assay and is well known in the art as an assay to identify proinflammatory molecules. Declarant states that proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. Declarant states that these proinflammatory molecules recruit cells like leukocytes which includes monocytes,

macrophages, basophils, and eosinophils. Declarant states that these cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. Declarant states that these processes are critical and tightly regulated via diapedesis and extravasation steps. Declarant concludes that proinflammatory molecules are useful in treating infections, as local administration of the proinflammatory polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing infection at a faster rate. Declarant points to MCP-1 and MCP-2 as being useful to cause neutrophils to extravasate, other CXC chemokines as being useful to activate neutrophils, and other CXC chemokines as being useful to cause chemotaxis of T lymphocytes. Declarant states that inhibitors of proinflammatory molecules are useful to treat diseases characterized by abnormal immune cell response. Declarant states that proinflammatory molecules with angiostatic properties are useful in treating tumors. Declarant states that the Miles assay was initially developed when researching the effect of histamine on the vascular system. Declarant states that subsequent workers have developed the assay into a quantitative one. This has been fully considered but is not found to be sufficient to overcome the rejection. The Miles assay is useful as a preliminary screen for potential proinflammatory molecules. Basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may e useful as a proinflammatory. For example, MCP-1 and MCP-2 are not only positive in the Miles assay, they were also shown to have the specific activity of causing the extravasation of

neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of activating neutrophils or being chemotactic for T lymphocytes. As was discussed in the previous Office Action, the state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a proinflammatory molecule with specific activities, as opposed to a basic irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989) is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation.

In point 10, Declarant states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). Declarant refers to Hirahara et al. (1993, Thrombosis Res.

71:139-148) as showing that FXIII stabilized microvasculature, leading to less permeability, and therefore may be useful in treatment of SHP. This has been fully considered but is not found to be sufficient to overcome the rejection. In the instant case, the claimed PRO protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable.

In point 11, Declarant states that the Miles assay was used by Senger et al. (1983, Science 219:983-985) to show that a secreted factor called VPF caused vascular permeability. This has been fully considered but is not found to be sufficient to overcome the rejection. Senger et al. set out to determine why vessels lining the peritoneal cavities of rodents with ascites tumors display markedly greater permeability than vessels in control animals. Senger et al. only conclude that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger et al. do not suggest that VPR can be considered a pro-inflammatory molecule useful for treatment of injury or infection.

In point 12, Declarant states that Yeo et al. (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results. Declarant states that VPF (VEGF) tested positive in the skin vascular permeability assay and then anti-VPF antibodies were used to quantify the amount of VPF in the DELFIA. Declarant states that the DELFIA assay has greater sensitivity. This has been fully considered but is not found to be sufficient to overcome the rejection. Yeo et al. do not assert that the DEFLIA assay or the Miles assay can be used to identify proinflammatory molecules

that can be used to treat injury or infection. Yeo et al. disclose that VPF may be the same protein as VEGF, which has been shown to be a mitogen specific for endothelial cells, and may promote tumor angiogenesis via its mitogenic activity for endothelial cells. However, the specific and useful activity of VEGF as an angiogenic factor was not identified by the Miles assay or the DEFLIA assay. Significant further research had to be conducted to identify this specific and substantial activity.

In point 13, Declarant reviews the skin vascular permeability assay and refers to Exhibit I as showing a positive reaction for a PRO polypeptide. This has been fully considered but is not found to be sufficient to overcome the rejection. It is not clear that the PRO polypeptide shown in the exhibit is the same PRO polypeptide of the instant claims. Furthermore, the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the claimed PRO polypeptide without resorting to undue experimentation.

In point 14, Declarant provides his expert opinion that the PRO polypeptide that shows activity in the skin permeability assay has specific, substantial and credible utilities. Declarant states that the application discloses that the results of the skin permeability assay were further analyzed by histopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation. Declarant concludes that the vascular permeability observed was not due to histamine release or endothelial cell damage. Declarant asserts that the PRO polypeptides testing positive in the assay are useful to enhance immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases. Declarant further states that angiogenic or

angiostatic properties of proinflammatory would find utility in controlling tumorigensis. This has been fully considered but is not found to be sufficient to overcome the rejection. The specification describes analysis of the results of the skin vascular permeability assay as follows:

> The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

As this quotation shows, the Declarant is not entirely correct with respect to the facts. The PRO polypeptides used in the assay are not further analyzed by histopathological examination **to rule out inflammation due to endothelial cell damage or mast cell degranulation**. In this specific case, human PRO331 was found to be an irritant to guinea pigs. Such *might* indicate that PRO331 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO331, e.g. that the human PRO331 protein has an epitope that the guinea pigs were pre-sensitized to. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO331. Accordingly, the only inflammation that could be treated using anti-PRO331 agents at the time the invention was made is that actually caused by PRO331, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting

from excess PRO331 based upon the results in the specification as originally filed). It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides. Finally, Declarant's comments regarding angiogenic or angiostatic activities of the PRO polypeptides is off-point, since these activities were not disclosed in the specification. Finally, it is noted that opinion declarations are evaluated for the reasonableness and validity of the opinion; however, no weight is given to an opinion on the ultimate legal conclusion in issue. Enablement is a legal conclusion. See *In re Lindall*, 155 USPQ 521; *In re Chilowsky*, 134 USPQ 515.

Due to the large quantity of experimentation necessary to determine how to use the claimed polypeptides other than as a polypeptide having the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells; the lack of direction/guidance presented in the specification regarding other uses, including uses related to vascular permeability activity as discussed above; the absence of working examples directed to PRO331 polypeptides having specifically useful pro-inflammatory activities; the complex nature of the invention; the contradictory state of the prior art; the unpredictability of what activities any uncharacterized protein may have; and the breadth of the claims which fail to recite useful functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claims 44-47 and 49-51 are allowable. Claims 39-43 are not allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number

is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER